and Section 112, second paragraph, rejections, Applicants have amended claims 35-38 by replacing "The use" with "The method" in order to render the claims in a condition for allowance.

35 U.S.C. § 103 Rejection

In the June 7, 2001 Office action, claims 14-28 and 34-38 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 91/04748 and Kappelhof et al. According to the Examiner, the WO 91/04748 reference teaches the use of growth factor inhibitors for the treatment of conditions associated with fibrosis and cell proliferation. The Examiner further asserts that the Kappelhof et al. reference teaches that after-cataract is a condition caused by the proliferation of lenticular epithelial cells. Applicants have carefully reviewed the Examiner's basis for the rejection of the above-referenced claims and believe that the Examiner may have misinterpreted the teachings of the cited references, as will be addressed below.

In response to the Section 103(a) rejection, Applicants respectfully submit that WO 91/04748 does not teach the use of inhibitors of transforming growth factor beta (TGFβ) to inhibit cell proliferation for the treatment of conditions associated with cell proliferation. Moreover, the WO 91/04748 reference does not report the *effect* of TGFβ or inhibitors of TGFβ on cell proliferation. In this regard, it is notable that although Examples I and IX of WO 91/04748 mention the ^{3}H-thymidine incorporation method used for measuring cell proliferation, the findings of these assays are not reported in the WO 91/04748 reference. Thus, WO 91/04748

would not have taught a person skilled in the art that inhibitors of TGFβ are useful for preventing cell proliferation.

Further, Applicants respectfully submit that it was well known in the art, prior to the priority date of the claims of the present application (November 19, 1993), that the biological effect of TGFβ is cell type specific and complex. The term "transforming growth factor," or indeed the term "growth factor" *per se*, cannot be interpreted literally to mean that a substance so named produces proliferation in all cells and under all conditions. Early research articles regarding TGFβ which were published in 1993, before the priority date of the claims of the present application, clearly taught that the effect of TGFβ on cell proliferation was variable and dependent on the cell type and culture conditions; however, inhibition of cell proliferation was thought to be its effect for most cell types (Rifkin *et al.*, 1993; Massague *et al.* 1992; Miyazono *et al.*, 1993).[1] In particular, there was a general consensus that the effect of TGFβ on the proliferation of epithelial cells was inhibitory (e.g., Massague *et al.*, 1992; and Rifkin *et al.*, 1993). A standard bioassay for TGFβ activity at that time, and today, depends on the ability of a given TGFβ-containing sample to inhibit cell proliferation in mink lung epithelial cells (Danielpour *et al.*, 1989).[2] A report that TGFβ had an inhibitory effect on proliferation of

---

[1] Rifkin *et al.* (1993), TGF-β: Structure, Function, and Formation, 70 Thrombosis and Haemostasis,177-179; Massague *et al.* (1992), Transforming Growth Factor-β, 12 Cancer Surveys, 81-103; Miyazono *et al.* (1993), Transforming Growth Factor-β: Latent Forms, Binding Proteins and Receptors, 8 Growth Factors, 11-22.

[2] Danielpour *et al.* (1989), Immunodetection and Quantitation of the Two Forms of Transforming Growth Factor-Beta (TGF-β1 and TGF-β2) Secreted by Cells in Culture, 138 Journal of Cellular Physiology, 79-86.

cultured lens epithelial cells was published in May 1993 (Kurasaka and Nagamato, 1993).[3] Therefore, before the priority date of the claims of the present application, a person skilled in the art would have expected that treating lens epithelial cells with TGFβ would cause inhibition of lens cell proliferation and that, conversely, applying an inhibitor of TGFβ would lead to an increase in lens cell proliferation.

Applicants respectfully submit that the present application is not based on a finding that inhibitors of TGFβ inhibit the proliferation of lens cells. Rather, the present invention arises out of the novel discovery that TGFβ induces lens cells to become abnormal in that they exhibit an altered morphology and other features that are characteristic of cells found in after-cataracts (and naturally occurring forms of cataract), and thus the surprising discovery that inhibitors of TGFβ can be used to prevent or control the formation of after-cataract. Accordingly, such a method of preventing or controlling after-cataract would not have been obvious to the skilled person before the priority date of the claims of the present application from the documents cited by the Examiner. Therefore, it is submitted that Claims 14-28 and 34-38 are not obvious in view of WO 91/04748 and Kappelhof et al. and that the claims should be allowed over the cited art.

---

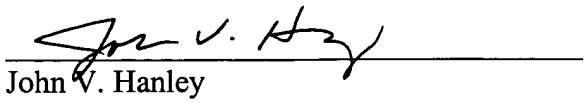
[3] Karasaka and Nagamoto (1993), Inhibitory Effect of TGF-β_2 in the TGF-β_2 Human Aqueous Humor on Proliferation of Bovine Lens Epithelial Cells, 34 Investigative Ophthalmology & Visual Science, 269-274.

CONCLUSION

Applicants have attempted to respond to each rejection in the Office action. In view of the above remarks, Applicants respectfully request that the application be reconsidered, the claims allowed and the application passed to issue.

Respectfully submitted,

FULWIDER PATTON LEE & UTECHT, LLP



John V. Hanley
Registration No. 38,171

JVH:LAK:bg
Enclosures
Howard Hughes Center
6060 Center Drive, Tenth Floor
Los Angeles, CA 90045
Telephone No.: (310) 824-5555
Facsimile No.: (310) 824-9696
Customer No. 24201

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claims 35-38 as follows:

35. (Amended) The [use] method according to claim 34 wherein the inhibitors of TGFβ are selected from proteins, glycoproteins and proteoglycans.

36. (Amended) The [use] method according to claim 35 wherein the protein inhibitors of TGFβ are selected from antibodies and peptide growth factors.

37. (Amended) The [use] method according to claim 35 wherein the glycoprotein inhibitors of TGFβ are selected from α_2-macroglobulin, laminin and collagen.

38. (Amended) The [use] method according to claim 35 wherein the proteoglycan inhibitors of TGFβ are selected from decorin, [heparan] heparin sulfate proteoglycans and biglycan.